Proposed synopsis on

DESIGNING, OPTIMIZATION AND EVALUATION OF ORAL JELLY FROM *CORDYCEPS MILLITERIS* DIRECTED AGAINST NEURODEGERATIVE DISORDER

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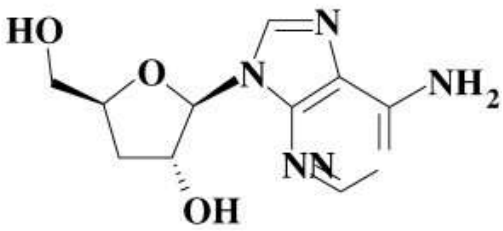
Introduction:

Cordyceps militaris is a potential harbour of bio-metabolites for herbal drugs and evidences are available about its applications for revitalization of various systems of the body from ancient times. Amongst all the species, Cordyceps militeris is considered as the oldest source of some useful chemical constituents. Besides their popular applications for tonic medicine by the all stairs of the community, the constituents of Cordyceps militeris are now used extensively in modern systems of medicine. The current survey records the mysterious potentials of Cordyceps militeris are boosting up the present herbal treatments, as well as gearing up the green pharmacy revolution, in order to create a friendly environment with reasonable safety. [1]

Evidence showed that the active principles of Cordyceps militeris are beneficial to act as pro-sexual, anti-inflammatory, anti-oxidant/anti-aging, anti-tumour/anti-cancer/anti-leukemic, anti-proliferative, anti-metastatic, immunomodulatory, anti-microbial, anti-bacterial, anti-viral, anti-fungal, anti-protozoal, insecticidal, larvicidal, anti-fibrotic, steroidogenic, hypoglacaemic, hypolipidaemic, anti-angiogenetic, anti-diabetic, anti-HIV, anti-malarial, anti-fatigue, neuroprotective, liver-protective, renal-protective as well as pneumoprotective, let alone their other synergistic activities, which let it be marketable in the western countries as over-the-counter medicine. A number of culture techniques for this mushroom have been noticed, for example, storage/stock culture, pre-culture, popular/indigenous culture.[2]

The prospects for herbal biotechnology regarding drug discovery using Cordyceps militeris delivering what it has promised are high, as the technology is now extremely more powerful than before. This study chiefly highlights the medicinal uses of the mushroom Cordyceps militeris including its culture techniques, also aiming to draw sufficient attention of the researchers to the frontier research needs in this context.



Cordycepin

(3′-deoxyadenosine)

The constituents of medicinal mushroom Cordyceps militaris, especially the anti-cancer agent cordycepin (3′-deoxyadenosine), are expected to play evolutionary roles in the pharmacognosy sector.[3]

C. sinensis was used more extensively than Cordyceps militeris and, their clinical applications are more or less similar. Although it is well known as a pro-sexual, anti-inflammatory and anti-cancer agent, it is presently using for many clinical cases like, insufficient pulmonary function, coughing, sputum, dizziness, memory failure, myodesopsia, vision failure, cold virus, in appetence, night sweat, pale face, pale lips, buzzing in the ears, toothache and loose teeth, insomnia and thirsty, cold.[6]

There is extensive literature on in vivo studies with cordycepin but these studies were generally conducted without validation of the various formulations, especially in terms of the solubility of cordycepin in the dosing vehicles used. Cordycepin is a promising drug candidate in multiple therapeutic areas and there is a growing interest in studies aimed at assessing the pharmacological activity of this compound in relevant animal disease models. It is likely many reported in vivo studies used formulations in which cordycepin was incompletely soluble. This can potentially confound the interpretation of pharmacokinetics and efficacy results

The species *Cordyceps Sinensis* is commonly called the Caterpillar Fungus and has probably been the most extensively studied species. It is a parasitic species that has caterpillar as its host. While it is mostly used medicinally, C. sinensis is also included in some food recipes. It has properties similar to ginseng and is said to be more potent.[8]

The first documented of its usage was in 620 AD, during the Tang Dynasty. It has been uses include strengthening of the body after exhaustion or long term illness, impotence, backaches and an antidote for opium poisoning. A lot of claims made of this fungus. Most of them have yet to be sufficiently investigated. In traditional Chinese medicine, Cordyceps has been used to treat respiratory and pulmonary diseases, e.g. renal, liver and cardiovascular diseases. It is also used in treating immune disorder and has been used in association with cancer chemotherapy treatments and surgery. It is also believed to be a remedy for

weakness and fatigue and often used as a "rejuvenator" for increase in energy. Successful treatment for impotence, acting as an aphrodisiac has also been demonstrated in clinical human testing. More can be said, but if even half of the listed treatments are, above, are true, it would indeed be a miracle mushroom.[9]

Objectives:

The objectives of the topic are as follows

- To attain higher bioavailability of Cordyceps extract.
- To identify the bioactivity of the chemical compound by Molecular Docking Technique.
- To Extract corycepine and formulate the Jelly by QBD approach.
- To evaluate dosage form for dose accuracy by analytical methods.
- To study Pharmacological activity by invivo studies.

Need of study:

The acceptance of the people towards mushroom is minimal due to be the natural *Cordyceps militeris* is expensive in the local market. In the present state, the production of cordycepin from the fruiting body of *Cordyceps militeris* is not likely to reach commercial levels due to some practical limitations. For example, Cordyceps militeris is very scarce in nature due to the requirements of specific hosts and strict growth environments. On the other hand, it is necessary to note that the chemical synthesis of cordycepin requires a complicated process resulting a lower content.

Nature is the source of all the raw materials that we need. About 30 years ago, most of the drugs were of herbal origin. A variety of reasons why people like to use natural medicines as it is evident that patients are getting even more distressed after using chemically synthesized drugs, rather than natural means like medicinal mushrooms that can conquer life-claiming diseases, leaving no side effects on human health. To maintain proper growth, the pharmaceutical industries need

To counterpart these problems the cordyceps extract would be easily administered with fixed doses using oral jelly formulation to attain the bioactivity in neurodegenerative Patients.

Materials and Methods:

The study can be prefabricated by following materials and methods

1. **Strain:** Cordyceps militeris strain provided by ICAR-Directorate of mushroom Reaserch, Solan
2. **Strain culture and cordycepin fermentation** Strain was inoculated onto potato dextrose agar (PDA) and grown at 21 ◦C for 10 days. Using a hole punch to create 3 mm diameter cakes, three cakes were inoculated in a triangular bottle containing seed liquid culture medium (20 g/L sucrose, 20 g/L peptone, 1 g/L K2HPO4, 0.5 g/L MgSO4·7H2O, pH not adjusted; 100 mL/250 mL) and oscillation cultured (26 ◦C, 130 rpm) for 84 h. Then the seed liquid was added at 3% to inoculate fermentation medium (100 mL/250 mL) (20 g/L glucose, 20 g/L fish peptone, 0.5 g/ L K2HPO4, 0.5 g/L MgSO4·7H2O, 0.5 g/L MnSO4, pH = 5.5). A mixed culture method (standing 3 days + shaking 22 d, 26 ◦C, 130 rpm) was used, and the raw cordycepin fermentation liquid was collected.[4]
3. **Extraction:** By preparing extract of *Cordyceps milliteris* by using different polar and nonpolar solvents.
4. **Evaluation:** The Qualitative and Quantative evaluation of corycepine by using different analytical tools.
5. **Neurodegerative studies** by using Pharmacological disease model for drug development of neurological disorder.

   5.1 The scopolamine model

   Scopolamine is a nonselective, competitive muscarinic receptor blocker. The scopolamine model has its roots in the cholinergic hypothesis of aging and

AD, and has played a major role in its construction, which we will recall briefly here.

Drachman and Leavitt administered scopolamine to healthy young volunteers, who then displayed a memory profile very close to that observed in elderly people.

Two to three years later, three independent research teams reported a decreased activity of choline acetyl-transferase (CAT), the enzyme responsible for acetylcholine (Ach) synthesis, in the cortex of AD patients. This decrease was shown to be correlated with brain lesions and clinical status. It was soon found that neuronal loss occurs in the forebrain basal nucleus of Meynert and medial septal nucleus, which are the source of neocortical and hippocampal cholinergic afferent fibers, respectively. In its early version, the cholinergic hypothesis stated nothing about etiological factors, did not address the additional roles that ACh dysfunction may play in other neurobehavioral disturbances of aging and dementia, and did not imply any exclusive or solitary involvement of the cholinergic system in age-related memory loss. It was a kind of "black box" model, in which an unknown pathophysiological process induces deficiency in various neurotransmission pathways thought to be responsible for the cognitive and behavioral aspects of aging and dementia. Despite obvious shortcomings (see references 17-20 for review and discussion), the cholinergic hypothesis legitimized the development of the cholinergic drugs we prescribe today and the administration of scopolamine as a model of investigation for AD research. [8]

5.2 The ketamine model

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. Its administration in order to produce a model is the correlate of the glutamatergic hypothesis of AD. Two, apparently opposite, glutamatergic hypotheses have been proposed. The excitotoxic hypothesis states that there is a

glutamatergic hyperactivity in AD. Domoic acid poisoning in humans was responsible for irreversible memory loss. Neuronal and astroglial glutamate transporter dysfunction in AD could result in excess glutamate in the synaptic cleft and in excitotoxic neuronal damage. This hypothesis is consistent with the beneficial effects of memantine and lamotrigine in AD patients. Some findings provide a link with the histopathological lesions that are the hallmarks of AD. Kainic acid injection in the rat leads to decreased neuronal amyloid precursor protein (APP) 695 mRNA owing to neuronal death, and increased astrocytic APP 770 mRNA, which has been found selectively increased in AD in comparison with other neurodegenerative disorders and associated with plaques. β- Amyloid sensitizes neurons to glutamate toxicity and also enhances glutamate release by macrophages. Furthermore, in neuronal culture, glutamate was shown to enhance tau gene expression and induce paired helical filaments similar to those found in AD. [11]

The hypoglutamatergic hypothesis has been extensively reviewed elsewhere (see Newcomer et al, in this issue). The ketamine model is its application. Ketamine is mainly used in the field of schizophrenia research to provoke psychotomimetic as well as cognitive effects. These studies did not all assess the same functions or use the same paradigm to assess a particular function. Despite this limitation, when these studies are summarized and the profile of ketamine effects compared with that of AD. The situation is the same as that for the scopolamine model: the functions affected by ketamine are affected in AD, but the reverse is not necessarily the case.[12]

Literature Survey:

1. Hardeep S. Tuli et al Reviewed the cordyceps Pharmacological and therapeutic potential with special reference to Cordycepin. Described cordyceps for ethno-pharmacological use. m this fungus comprises a novel bio-metabolite called as Cordycepin (30deoxyadenosine) which has a very potent anti-cancer, anti-oxidant and anti-inflammatory activities. The current review discusses about the broad spectrum potential of Cordycepin including biological and pharmacological actions in immunological, hepatic, renal, cardiovascular systems as well as an anti-cancer agent. The article also reviews the current efforts to delineate the mechanism of action of Cordycepin in various bio-molecular processes. Also described process of host infection and cultivation of cordyceps fungus and Molecular studies of genes isolated from Cordyceps sp.[3]

2. Young Ock Kim et al investigated studies to explore the therapeutic properties and neuroprotective effect of the Cordyceps militaris on ischemic brain neuronal injury, impairment of memory and learning in experimental rats induced by a global cerebral ischemia-reperfusion injury in WISTAR rats. Vascular Dementia with transient global brain injuries induced by a four-vessel occlusion (4-VO) in WISTAR rats. Further, donepezil (5 mg/kg) and Cordyceps militaris was (100 and 300 mg/kg, p.o.) were orally administered for 7 days in 4-VO WISTAR rats. Cordyceps militaris has the ability to improve memory impairments due to global cerebral ischemia and scopolamine-induced memory deterioration. Our present findings suggest that Cordyceps militaris may be a potential candidate for the neuroprotection of hippocampus and the recovery of various vascular dementia or neuro-inflammatory disorders.[1]

3. Karol Jerzy J¸edrejko et al reviewed the article Cordyceps militaris: "An Overview of Its Chemical Constituents in Relation to Biological Activity in this review article" narrated This review aims to present the chemical composition and medicinal properties of Cordyceps militaris fruiting bodies and mycelium, as well as mycelium from in vitro cultures. The analytical results of the composition of Cordyceps militaris grown in culture media show the bioactive components such as cordycepin, polysaccharides, γ-aminobutyric acid (GABA), ergothioneine and others described in the review. he also narrated Recent scientific reports indicate the potential of cordycepin in antiviral activity, particularly against COVID-19.[2]

4. Yujiang Ji et al synthesized the Gold Nanoparticles by Green Synthesis using a *Cordyceps militaris* extract and their antiproliferative effect in liver cancer cells (HepG2). In this research they investigated the gold nanoparticles with Cordyceps militaris on the hepatocellular carcinoma HepG2 cells. The synthesized gold nanoparticles stability and integrity was studied at different time intervals. The gold nanoparticles potentially halt the growth of the HepG2 cells at the IC50 concentration between 10lg and 12.5 lg/ml. The HR-TEM and XRD revealed the size and shape of the synthesized gold nanoparticles. The size of the gold nanoparticles was about 1520nm and the shape of gold nanoparticles was face-center-cubic structure. The FT-IR results proved that the gold nanoparticles contain hydroxyl and alkynes groups. The gold nanoparticles extract develops ROS and cause damage to the mitochondrial membrane potential in the hepatocellular carcinoma HepG2 cells. The gold nanoparticles extract tends to initiate the apoptosis by activating the Bax, Bid, caspases and inhibits the activation anti-apoptotic bcl-2 in the HepG2 cells. Our results concluded that the gold nanoparticles with Cordyceps militaris would be an efficient chemotherapeutic drug against the hepatocellular carcinoma cells.[4]

5.Eunhyun Choi et al elaborated Antithrombotic and Antiplatelet Effects of Cordyceps militaris. He investigated whether the antiplatelet effect of ethanol extract of cultured Cordyceps militaris (CMEE) with FeCl3-induced arterial thrombosis model. He observed that CMEE exhibited a significant inhibitory effect against ADP and collagen-induced platelet aggregation. However, there were no significant differences in prothrombin time (PT) and activated partial thromboplastin time (aPTT). These results suggest that antithrombotic activity of CMEE is related to antiplatelet effect rather than anticoagulation effect, and CMEE may be a positive effect on improving blood circulation against vessel injury and occlusion.[11]

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